Opinion

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Routes of Neuroinflammation Autophagy and Calcium Dependent Mechanisms in Traumatic Brain Injury

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Neuroinflammation, immunosuppression, autophagy, and calcium-dependent mechanisms, are those cellular events, which occurred at the site of injury. Prolonged and delayed neuroinflammation promote macrophages and as a result, the activation of resident microglia cells comes into existence. The chain of these biological transformations enhances astrogliosis. The improper connected axonal and increased axonal transport proteins in the node originated prolonged swelling of injured axons and induced apoptotic cell death of neurons [1]. The association of axonal damage in the corpus callosum and infiltration of neuroinflammatory cells distressed degradation of axons, deformation of white matter, damage of oligodendrocytes, and blood vasculature [2]. Glial scar and myelin-associated axonal growth inhibitors, originated insults in the CNS, promote the activities of astrocytes, including activation and proliferation that induce astrogliosis and make the situation more complex [3]. Activated astrocytic allied with functioning features of microglia, fibroblasts, oligodendrocytes, and meningeal cells. As a result, scar-like assemblies come into existence. It is like a barrier that initiates obstacles in the process of axonal regeneration. The intrinsic mitochondrial pathway involved in apoptotic cell death is initiated by caspase-dependent mechanisms [4]. After mitochondrial depolarization, these pathways participate in the interaction phenomenon of TNF and FAS on the cell surface, meanwhile, their specific receptors also contribute to it. Cytochrome c, apoptotic activating protein-1, and ATP existed in the cytosol-shaped ATP-dependent complex [5]. These cellular events transformed the caspase-dependent downstream signaling by prompting caspase 8 and 9. These transformations initiate the process of breaking down caspase. Meanwhile, mitochondrial proteins trigger downstream signaling molecules after translocation into the nucleus, and as a result, DNA damage transpired [6]. These specific events further promote chromatin condensation in neuronal and glial cells. Impairment of autophagy and lysosomal pathways, Autophagy governed cyto protection, cell stability, and survival. By eliminating abnormal intracellular proteins or damaged organelles during the stressful situation of the cell, the process of autophagy controlled these cellular events. The role of autophagy is also important in inflammation, apoptotic cell death, and adaptive immune responses. One of the subtypes of autophagy, i.e., macro autophagy, deals with damaged organelles and responds to the activities of autophagosomes [7]. The lysosomes participated in these events and initiated proteolytic degradation. The autophagy-lysosome pathway is the key component of TBI. However, during brain injury, autophagic flux improved neuronal survival, upgraded neurobehavioral function, controlling inflammation and gliosis [8]. The event of impairment of autophagic flux happened and was well followed by the pathological accumulation of autophagosomes neuronal cell death. These unhealthy and unnatural cellular events enhanced the severity of trauma.

Activated protein kinase C and NMDA receptors enhance the Ca^{2+} influx into postsynaptic neurons. Later on, the AMPA receptors uphold calcium-dependent mechanisms to catalyze the MAPK pathway. These biological transformations increase the production of reactive oxygen and nitric oxide [9] These biological events intensify secondary cell injury. In presence of activated phospholipase C/inositol-1,4,5-triphosphate, the secretion of Ca^{2+} from intracellular stores started and reached the cytosol. These calcium ions activate signaling

cascades at the site of injury. But, the extreme concentration of Ca^{2+} in the cytosol disturbs the normal activities of proteins, and finally, these cellular events induce apoptotic cell death. The association of Ca^{2+} and ROS dysregulates the functioning of mitochondrial and ROS homeostasis [10] The excessive stimulation of glutamate receptors induces oxidative stress and excitotoxic cell death. Disturbances in the normal functioning of mitochondria promote the interruption of the electron transport chain and finally upset oxidative phosphorylation processes. These unwanted happenings interrupt the proceedings of metabolic reactions for cell survival and regulation of the calcium cycle. The opening of mitochondrial permeability transition pore initiates conformational changes in the inner membrane, as a result, an increase in the inner membrane permeability transpired. These changes in the features of permeability further contribute to mitochondrial pathology and analysis of these features revealed the route of swelling and structural damage in the cristae membrane [11]. These insignificant transformations decrease membrane potential that plays a crucial role in apoptotic cell death. Various cellular events, such as enzymatic processes, activated neutrophils, excitotoxic pathways, and dysfunctional mitochondria generate endogenous ROS and free radicals. The accumulation of Ca^{2+}triggered nitric oxide synthases and enhanced NO percentage [12].

These unwanted cellular events induce oxidative damage. Enhanced permeability of mitochondria membrane and breakdown of membrane proteins disturbed the normal flow of ion transportation. Therefore, irregularities in Ca^{2+}accumulation induce prolonged excitotoxicity and final disturbance in brain plasticity, and cerebral blood flow originates [13]. Overall, the rate of immunosuppression increased [14]. Herein, the author expresses the role of neuroinflammation, autophagy, and calcium concentration in traumatic brain injury and specifically underlines the disturbances that transpired in the proceedings of metabolic reactions and how these cellular events are important for cell survival. The elucidation of these cellular events can be fruitful for searching for new therapeutic targets.

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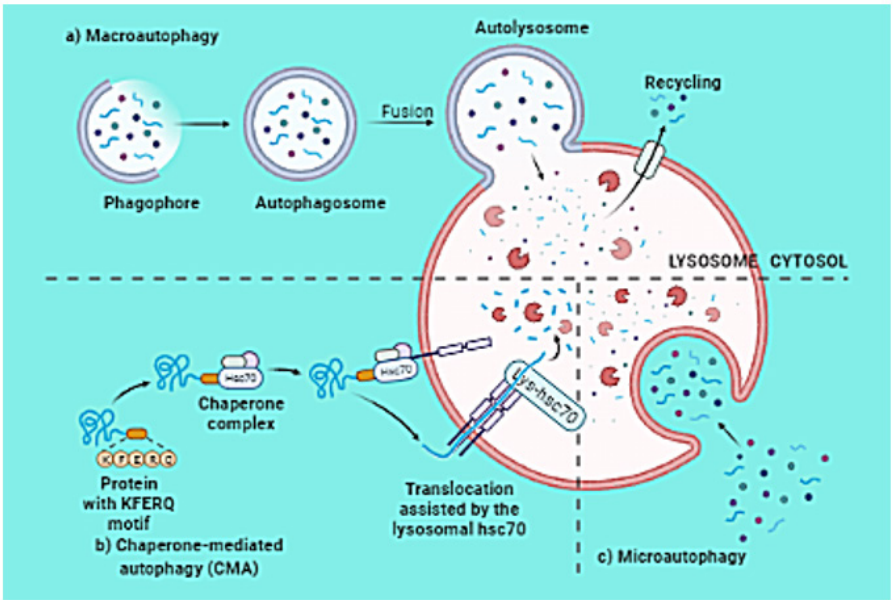

Figure 1: Illustration of the Phenomenon of an Autophagy-Lysosome Pathway.

Availability of Data and Materials

Wherever necessary, relevant citations are included in the reference section.

Competing Interest

The author has declared that no competing interest exists.

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